FACULTÉ DE MÉDECINE

FÉCONDITÉ ET MORTALITÉ INFANTILE DANS LA DYSTROPHIE MYOTONIQUE AU SAGUENAY-LAC-ST-JEAN (QUÉBEC, CANADA).

TO-NGA DAO

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RÉSUMÉ

Une étude cas-témoins a été réalisée à partir de 373 personnes atteintes de dystrophie myotonique (DM) mariées au Saguenay-Lac-St-Jean entre 1855 et 1971. Leur fécondité et la mortalité infantile (jusqu'à 15 ans) parmi leurs enfants ont été analysées. Le nombre moyen d'enfants nés des personnes atteintes n'était pas significativement différent de celui des témoins ($p>0.05$). Les hommes atteints de DM ont eu plus d'enfants que les femmes atteintes bien qu'ils aient commencé à retarder leur mariage dès 1921. Une augmentation significative a été trouvée dans le taux de mortalité durant la première semaine parmi les enfants des mères atteintes de DM comparativement aux taux de mortalité des enfants issus de mères témoins et de pères atteints ($p<0.01$). La fécondité et la mortalité infantile ont décliné substantiellement dans le groupe DM et dans le groupe contrôle durant la période d'observation.

SUMMARY

A case-control study was performed on 373 individuals with myotonic dystrophy (MD) married in Saguenay-Lac-St-Jean between 1855 and 1971. Their fertility and the infant mortality (up to 15 years old) among their children were analyzed. The mean number of children born to MD and control individuals was not different ($p>0.05$). MD males had more children than MD females, although they have started delaying their marriage since 1921. A significant increase was found in the rate of deaths during the first week among the children born to MD mothers compared to control mothers and MD males ($p<0.01$). Fertility and infant mortality fell significantly in both the MD and control groups during the period of observation.

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INTRODUCTION GÉNÉRALE

La dystrophie myotonique (DM) est une maladie autosomale dominante dont la prévalence est estimée à 1 pour 529 habitants au Saguenay-Lac-St-Jean (SLSJ). Il s'agit de la plus forte prévalence connue au monde pour cette maladie. C'est pourquoi une recherche intensive menée dans la région essaie de mieux connaître les aspects cliniques, historiques, démographiques et socio-économiques de la dystrophie myotonique alors que d'autres essaient d'identifier et de cloner le gène.

Ce mémoire s'inscrit donc dans ce cadre de recherche. En effet, l'une des questions qui n'a pas encore reçu de réponse est la suivante: Pourquoi la dystrophie myotonique est-elle si fréquente au SLSJ? D'où l'intérêt d'étudier les paramètres démographiques tels que fécondité et mortalité infantile.

Bien que deux études menées au SLSJ aient déjà essayé de déterminer si la fécondité dans les familles de dystrophie myotonique était modifiée par rapport à la population générale, la présente étude, sujet de ce mémoire, utilise une approche différente, à savoir une étude cas-témoins. De plus, elle s'intéresse à la mortinatalité et à la mortalité infantile en utilisant la même approche.

CHAPITRE I.

LA MALADIE ET LES OBJECTIFS DE RECHERCHE.

I.1. LA MALADIE.

I.1.1. Historique.

La dystrophie myotonique (DM), encore appelée dystrophia myotonica ou myotonia atrophica, est une maladie autosomale dominante qui fut décrite de façon non équivoque en 1909 d'une part par Steinert, et, d'autre part, par Batten et Gibb. Dans son article, Steinert rapporte neuf patients qui présentaient de la myotonie, une faiblesse et une atrophie musculaire distale, une faiblesse des muscles faciaux et une atrophie des muscles sterno-cléido-mastoïdiens. Un malade avait une voix nasillarde et un autre une atrophie testiculaire. Il présenta des études morphologiques. C'est pourquoi, la dystrophie myotonique est aussi connue sous le nom de maladie de Steinert.

Il est évident que Steinert (1909) et Batten et Gibb (1909) ne sont pas les premiers à avoir décrit des cas de DM. Cependant, depuis la publication de Thomsen (1876) sur la myotonie congénitale (maintenant connue sous la nom de maladie de Thomsen) jusqu'aux travaux de Steinert, une certaine confusion existait entre les deux maladies, certains cas étant considérés comme étant des cas de maladie de Thomsen atypique ou encore des cas de myotonie congénitale avec atrophie musculaire (Erb 1886; Curschmann 1906). Il n'en demeure pas moins que plusieurs cas publiés entre 1876 et 1909 sont indéniablement des cas de DM (Dana 1888; Hoffman 1900; Rossolino 1902; Passler 1906; Furnrohr 1907).

Dès 1911, Greenfield reconnaît que les cataractes font partie du tableau clinique de la dystrophie myotonique. En 1912, Curschmann considère que les cataractes et l'atrophie testiculaire sont des indicateurs d'un trouble endocrinien généralisé et que la dystrophie myotonique devrait donc être considérée comme une maladie multisystémique plutôt qu'une maladie musculaire (Curschmann 1912, 1925, 1936).

La présence de troubles du rythme cardiaque a été reconnue très tôt (Steinert 1909; Griffith 1911). Depuis que l'usage de l'électrocardiographie s'est répandu, les troubles de conduction cardiaque sont apparus plus fréquents que soupçonnés (Evans 1944; De Wind et Jones 1950).

Bien que les aspects héréditaires aient été débattus dès 1909, ce n'est qu'en 1923 que Adie et Greenfield ont classé la DM parmi les maladies neurologiques dégénératives héréditaires. De plus, le caractère dominant de la maladie ne fut établi qu'en 1948 par Bell et par Thomasen.

I.1.2. Prévalence de la dystrophie myotonique.

La dystrophie myotonique est la forme de dystrophie musculaire la plus fréquente de l'âge adulte. Elle présente une distribution mondiale; elle a été décrite dans un grand nombre de pays et dans toutes les races (Harper 1989). La maladie a une prévalence similaire dans la plupart des populations étudiées à l'exception de la population

canadienne française du Saguenay-Lac-St-Jean qui possède la prévalence la plus élevée au monde (1/529 habitants) (Mathieu et al. 1990) (Tableau I.1).

I.1.3. Biologie moléculaire de la DM.

Dès 1972, il est devenu évident que le gène de la dystrophie myotonique était situé sur un seul locus lié au locus Sécréteur et à celui du groupe sanguin Luthéran (Renwick et al. 1971; Harper et al. 1972a). Cependant, comme ces deux loci n'avaient pas encore été localisés, la localisation du gène de la DM sur un chromosome déterminé restait inconnue.

Ce n'est qu'en 1983 que la liaison du gène de la DM à d'autres loci (C3, PEPD) fut décrite, ce qui permit la localisation du gène de la DM sur le chromosome 19 (McAlpine et al. 1976; Whitehead et al. 1982; O'Brien et al. 1983; Eiberg et al. 1983).

Depuis 1983, le nombre de marqueurs étroitement liés au gène de la DM n'a cessé d'augmenter, ce qui a permis d'utiliser certains d'entre eux pour le dépistage des porteurs asymptomatiques et le diagnostic prénatal (Meredith et al. 1986; Meredith et al. 1988; Norman et al. 1989).

La figure I.1. montre l'agencement des principaux marqueurs situés sur le chromosome 19 en relation avec le locus de la dystrophie myotonique (Brook et al. 1984; Laberge et al. 1985; Shaw et al. 1985; Bartlett et al. 1987; Friedrich et al. 1987; Harley et al. 1988; Shaw et

Tableau I.1

Prévalence de la dystrophie myotonique dans diverses régions.

Régions	Prévalence	Références
Turin, Italie	1/47619	Pinessi et al. 1982
Veneto, Italie	1/37313	Mostacciuolo et al. 1987
Suisse	1/20408	Klein 1958
Allemagne de l'Ouest	1/18182	Grimm 1975
Irlande du Nord	1/41667	Lynas 1957
Japon	1/36630	Takeshita et l981
Afrique du Sud	1/6993	Lotz et Van der Meyden 1985
Rochester, MN, USA	1/30303	Kurland 1958
SLSJ, Québec, Canada	1/529	Mathieu et al. 1990

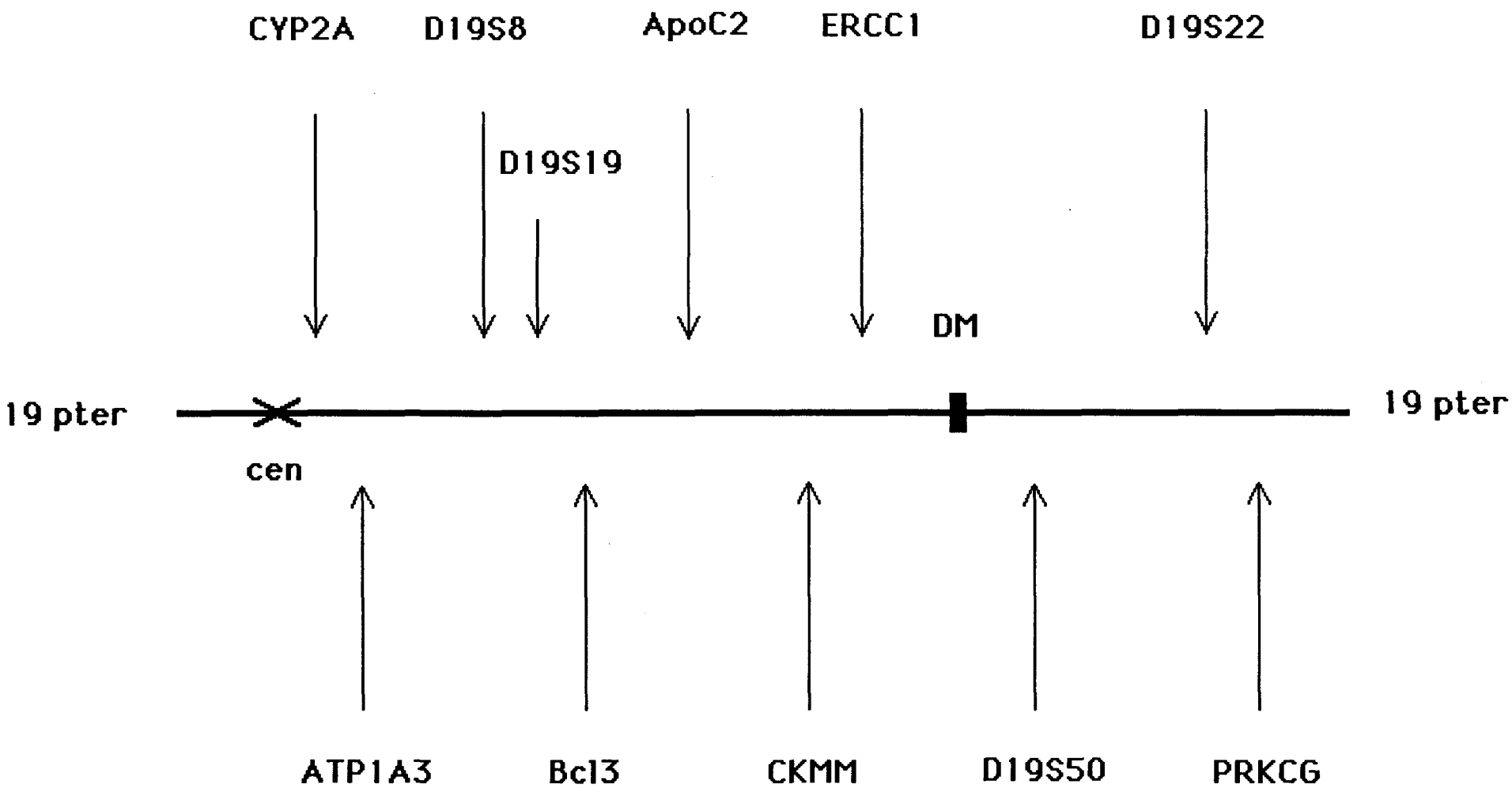

Figure I.1. Agencement des principaux marqueurs situés sur le chromosome 19 en relation avec le locus de la dystrophie myotonique.

Harper 1989; Myklebost et Rogne 1989; Brunner et al. 1989; Korneluk et al. 1989a,b; MacKenzie et al. 1989; Smeets et al. 1990; Brook et al. 1991).

Au Québec, une analyse de liaison entre les loci de la DM et de l'ApoE a été réalisée dans 11 familles. Un lod score de 19,00 avec une fraction de recombinaison de 0 a été trouvée (Laberge et al. 1985; Thibault et al. 1989). La détermination des phénotypes de l'apolipoprotéine E a permis de constater que deux phénotypes (E4:2 et E4:3) étaient préférentiellement associés à la dystrophie myotonique ($p<0,05$) (Moorjani et al. 1989). Une diminution du cholestérol LDL et une augmentation des triglycérides et du cholestérol VLDL ont été constatées dans le groupe DM par rapport à un groupe contrôle (Moorjani et al. 1989).

Un déséquilibre de liaison a été mis en évidence dans la population canadienne française atteinte de dystrophie myotonique entre plusieurs marqueurs ADN et le locus de la DM (Korneluk et al. 1989a, b; Laberge 1989; MacKenzie et al. 1989).

I.1.4. Aspects cliniques

I.1.4.1. Age d'apparition des symptômes, âge au décès, sévérité et anticipation.

Il est souvent très difficile de préciser avec exactitude l'âge d'apparition des premiers symptômes de la maladie, celui-ci pouvant

précéder de plusieurs années l'âge au diagnostic. Bien que l'âge médian d'apparition se situe aux environs de 20 à 25 ans, il peut varier considérablement, allant de 7 ans (pour les formes infantiles) à plus de 60 ans (Bell 1948; Thomasen 1948; Klein 1958; Harper 1977). Des résultats semblables ont été obtenus dans une série de 162 patients du SLSJ, l'âge d'apparition s'échelonnant de 5 à 48 ans avec une moyenne de 21,2 ans (Mathieu et al. 1991).

Les données concernant l'âge au décès dans la dystrophie myotonique sont plus rares. De plus, elles sont sujettes à un biais important en ce sens que la mortalité néonatale due aux formes congénitales et celle de patients atteints plus modérément n'ont pas été prises en considération. L'âge moyen au décès publié à ce jour varie de 43,5 à 50,6 ans selon les sources (Bell 1948; Thomasen 1948; Klein 1958; Grimm 1975).

Le degré d'atteinte neuro-musculaire ou sévérité de la maladie a été étudié par quelques auteurs (Thomasen 1948; Klein 1958). L'étude la plus complète a été réalisée au SLSJ (Mathieu et al. 1991). Celle-ci a montré que la sévérité de la maladie était très variable d'une personne à l'autre. De plus, elle était indépendante du sexe du patient, du sexe du parent transmetteur, et de l'âge d'apparition des premiers symptômes. Les répercussions socio-économiques ont été particulièrement bien étudiées par Perron et al. (1989) qui ont montré que la proportion des personnes n'ayant pas de travail était plus élevée dans le groupe atteint de dystrophie myotonique que dans la population générale.

Le phénomène d'anticipation a été évoqué pour la dystrophie myotonique. Rappelons qu'on appelle anticipation le phénomène par lequel une maladie est transmise sur plusieurs générations avec une sévérité accrue à chaque génération. Le principe de l'anticipation dans la DM avait été émis par Penrose en 1948 et repris plus récemment par Howeler et al. (1989). Il existe cependant de nombreux biais principalement dus à la grande variabilité de la sévérité de la maladie (Penrose 1948; Harper 1989). Dès lors, il n'est pas encore prouvé que l'anticipation est un véritable phénomène biologique dans la dystrophie myotonique.

I.1.4.2. Atteinte musculaire.

I.1.4.2.1. Musculature striée.

La présence d'une myotonie associée à une faiblesse puis atrophie musculaire présentant une distribution caractéristique permet de poser en toute confiance le diagnostic de dystrophie myotonique dans un grand nombre de cas.

La myotonie est un phénomène qui consiste dans un retard du relâchement musculaire après une contraction. Cette myotonie peut être mise en évidence en demandant au malade de serrer la main de quelqu'un ou encore en percutant l'éminence thénar (Harper 1989). La myotonie est un signe clinique qui est plus marqué chez les patients ayant peu de faiblesse et d'atrophie musculaire (Harper 1989).

La faiblesse des muscles faciaux est l'un des signes les plus précoces et les plus constants de la dystrophie myotonique (Harper 1977; Harper 1989; Bouchard 1989; Mathieu et al. 1991). Parmi les muscles de la tête et du cou les plus fréquemment touchés, on note les muscles faciaux superficiels, le muscle releveur de la paupière, les muscles temporaux et sterno-cléido-mastoïdiens et les muscles de la langue et du palais. L'atteinte de ces différents muscles est responsable d'un faciès particulier, de l'aspect décharné du cou, de la ptose des paupières et d'une voix nasillarde (Harper 1989; Bouchard 1989; Mathieu et al. 1991).

La faiblesse musculaire au niveau des membres est un signe très fréquent dans la dystrophie myotonique. Cette faiblesse concerne d'abord les muscles distaux des membres supérieurs et inférieurs, ce qui entraîne une diminution de la force des poignets et une faiblesse dans la dorsiflexion des pieds (Harper 1989; Bouchard 1989; Mathieu et al. 1991). L'atteinte des muscles proximaux est parfois présente lors de l'évolution de la maladie; elle est cependant un signe tardif (Mathieu et al. 1991).

Pour mieux décrire le processus d'atteinte musculaire progressive, on s'est attaché à développer une échelle, appelée grade neuro-musculaire, à la Clinique des maladies neuro-musculaires de l'Hôpital de Chicoutimi (Tableau I.2) (Mathieu et al. 1991).

Tableau I.2

Echelle du grade neuro-musculaire développé à la Clinique des maladies neuro-musculaires de l'Hôpital de Chicoutimi.

Grade	Description du grade
1	Pas de signe clinique de l'atteinte musculaire (diagnostic fait par électromyographie, marqueurs ADN ou examen à la lampe à fente).
2	Signes d'atteinte légère (myotonie, faiblesse/atrophie des muscles de la tête et du cou, voix nasillarde, pas de faiblesse distale).
3	Faiblesse distale (Pas de faiblesse proximale à l'exception d'une faiblesse isolée des triceps).
4	Faiblesse proximale légère ou modérée.
5	Faiblesse proximale sévère (Confiné au fauteuil roulant pour de courtes ou de longues distances).

I.1.4.2.2. Musculature lisse.

Bien que l'atteinte des muscles striés soit la mieux documentée, les muscles lisses ne sont pas épargnés par la dystrophie myotonique. Cependant, le degré d'atteinte est très variable d'un organe à l'autre (Chiu et Englert 1962; Harvey et al. 1965; Schuman et al. 1965; Maze et al. 1973; Theodore et al. 1979).

La dysphagie due à une faiblesse de la musculature pharyngée et oesophagienne est un symptôme retrouvé chez un grand nombre de malades à un stade avancé (Hughes et al. 1965; Schuman et al. 1965; Garrett et al. 1969; Pettengell et al. 1985).

La lithiase vésiculaire est une association fréquente de la dystrophie myotonique. On a tenté d'expliquer cette formation de calculs par une fonction déficiente de la vésicule biliaire, ou encore par un défaut dans le métabolisme du cholestérol et des acides biliaires (Chiu et Englert 1962; Harvey et al. 1965; Theodore et al. 1979).

I.1.4.3. Atteinte cardiaque.

L'atteinte cardiaque a été notée dans la dystrophie myotonique par Griffith (1911) qui rapportait une bradycardie sévère chez un malade de 48 ans. Depuis, tous les auteurs ont décrit une atteinte cardiaque chez 20 à 30% des patients. Ces troubles consistent principalement en un prolapse de la valve mitrale ou des troubles de conduction (Evans 1944; Church 1967; Salomon et Easley 1973; Clements et al. 1975; Grigg

et al. 1985).

Les anomalies électrocardiographiques sont très fréquentes dans la dystrophie myotonique (Church 1967; Bulloch et al. 1967; Clements et al. 1975; Grigg et al. 1985; Nguyen et al. 1988). Elles consistent notamment en troubles non spécifiques de la repolarisation, en blocs de branche et en blocs auriculo-ventriculaires qui peuvent être complets, nécessitant l'implantation d'un pacemaker (Church 1967; Bulloch et al. 1967; Thomson 1968; Clements et al. 1975).

La prolapse de la valve mitrale est une anomalie communément trouvée dans la dystrophie myotonique, sa fréquence variant de 25 à 30% selon les études (Winters et al. 1977; Gottdiener et al. 1982; Streib et al. 1985).

I.1.4.4. Atteinte ophtalmique.

Outre la ptose des paupières supérieures, la myotonie et la faiblesse des muscles extra-oculaires, la dystrophie myotonique est responsable de cataractes présentant des caractéristiques très spécifiques à la maladie (Greenfield 1911; Vogt 1921).

Bien que les modifications au niveau du cristallin soient le signe le plus fréquemment observé en dehors de l'atteinte neuro-musculaire, il ne semble pas y avoir de relation entre le degré de l'atteinte musculaire et le degré de l'atteinte ophtalmique (Bell 1948; Thomasen 1948; Lynas 1957; Klein 1958; Harper 1989). En effet, certains patients

présentent une cataracte sévère alors que l'atteinte musculaire est encore minime, voire même inexistante alors que d'autres, qui sont à un stade musculaire avancé, n'ont encore aucune anomalie cristalline.

L'atteinte du cristallin est progressive et mise en évidence à l'examen avec la lampe à fente. Les premiers signes non équivoques consistent en des opacités colorées localisées principalement dans les régions sous-capsulaires postérieures (Vos 1938; Buschke 1943; Junge 1966).

I.1.4.5. Autres problèmes reliés à la maladie.

La symptomatologie étant très variable d'un malade à l'autre, d'autres signes cliniques ou problèmes peuvent être rencontrés avec plus ou moins de régularité. C'est ainsi que la calvitie frontale et temporale est très fréquente chez les hommes atteints mais pas chez les femmes (Lynas 1957).

De nombreux auteurs soulignent que la dystrophie myotonique est un facteur de risque lors d'anesthésie. On a décrit plusieurs complications allant jusqu'au décès (Dundee 1952; Kaufman 1960; Caughey et Myrianthopoulos 1963; Tsueda et al. 1975; Phillips et al. 1984; Aldridge 1985; Moore et Moore 1987; Mathieu et al. 1991 [soumis]).

I.1.5. Anomalies endocriniennes et reproductives.

I.1.5.1. Anomalies endocriniennes.

L'atrophie testiculaire est un signe souvent retrouvé chez les hommes atteints de dystrophie myotonique (Thomasen 1948; Klein 1958). Les changements anatomopathologiques consistent en une dégénérescence des cellules et des tubules séminifères avec une hyperplasie des cellules de Leydig (Thomasen 1948; Marshall 1959; Caughey et Myrianthopoulos 1963).

Harper et al. (1972b) ont publié une étude à propos des taux plasmatiques de gonadotrophines mesurées par radio-immuno-essai chez 39 hommes atteints de dystrophie myotonique. Ils ont constaté que les taux de FSH étaient élevés chez tous les patients alors que ceux de la LH étaient normaux à légèrement augmentés. Par contre, chez un grand nombre de malades, le taux de testostérone était abaissé. Des résultats similaires ont été rapportés par Sagel et al. (1975) et par Takeda et Ueda (1977).

Chez la femme, il ne semble pas exister d'hypogonadisme ni de dysfonctionnement gonadique (Marshall 1959; Sagel et al. 1975).

Bien que plusieurs auteurs aient établi une association entre dystrophie myotonique et diabète (Caughey et Brown 1950; Stanbury et al. 1954: Jacobson et al. 1955), les études basées sur de grandes séries de patients semblent infirmer l'existence d'une telle relation (Thomasen

1948; Klein 1958; Harper 1989). Par contre, de nombreux chercheurs ont mis en évidence une réponse insulinique augmentée lors des tests de surcharge en glucose. (Huff et al. 1967; Gorden et al. 1969; Walsh et al. 1970; Barbosa et al. 1974; Cudworth et Walker 1975).

Les autres fonctions endocriniennes ne semblent pas être touchées par la dystrophie myotonique, notamment la thyroïde (Drucker et al. 1961; Steinbeck et Carter 1982), les glandes surrénales (Drucker et al. 1961; Caughey et Myrianthopoulos 1963; Bernard-Weil 972) et les glandes parathyroïdes (Drucker et al. 1961; Caughey et Myrianthopoulos 1963).

I.1.5.2. Anomalies obstétricales

De nombreuses complications durant la grossesse sont associées à la dystrophie myotonique (Shore 1975; Harper 1989; Paris et al. 1989).

Le premier trimestre est marqué par une forte augmentation du taux d'avortement spontané (O'Brien et Harper 1984; Harper 1989). Une complication majeure de la grossesse est l'hydramnios dû à une déglutition anormale du foetus (Dunn et Dierker 1973). On retrouve un hydramnios seulement si la mère et le foetus sont atteints (Paris et al. 1989).

L'échographie permet de visualiser certaines anomalies squelettiques foetales ainsi qu'une réduction des mouvements foetaux (Paris et al. 1989).

L'atteinte de la musculature utérine peut être responsable des contractions inefficaces suivies d'une période de relaxation prolongée lors du travail et de l'accouchement, mais aussi de rétention placentaire et d'hémorragies post-partum (Sciarra et Steer 1961; Shore et MacLachlan 1971; Webb et al. 1978; O'Brien et Harper 1984a).

Une seule étude d'envergure a été réalisée à ce jour sur la grossesse et l'accouchement dans la DM (O'Brien et Harper 1984a). Elle a mis en évidence plusieurs problèmes obstétricaux tels que rétention placentaire, placenta praevia, décès néonataux et hydramnios.

I.1.5.3. Formes congénitales et infantiles.

Alors que la dystrophie myotonique a d'abord été considérée comme une maladie de l'âge adulte, Vanier, en 1960, décrivait six enfants atteints de DM chez qui la maladie semblait être d'origine congénitale. Depuis, plusieurs auteurs ont décrit cette forme congénitale de DM (Dodge et al. 1966; Calderon 1966; Aicardi et al. 1974; Harper 1975a,b; O'Brien et Harper 1984b).

Il est aussi très bien établi que la grande majorité des enfants atteints de la forme congénitale sont issus de mères atteintes de dystrophie myotonique ou porteuses du gène (Vanier 1960; Harper 1975a,b; O'Brien et Harper 1984b). Dès lors, la forme congénitale semble résulter de la combinaison du gène de la dystrophie myotonique et d'un quelconque facteur maternel (Harper 1989).

Les principaux signes cliniques de la forme congénitale de DM sont résumés dans le tableau 1.3 (Harper 1989). La forme congénitale représente donc une entité clinique distincte de la forme adulte.

Il existe aussi une forme infantile qui présente les caractéristiques de la forme adulte mais qui commence dans l'enfance (O'Brien et Harper 1984b).

I.2. OBJECTIFS DE RECHERCHE.

I.2.1. Objectif général.

- Contribuer à la compréhension de la prévalence élevée de la dystrophie myotonique au Saguenay-Lac-St-Jean.

I.2.2. Objectifs spécifiques.

- Analyser la fécondité des personnes atteintes de DM au SLSJ.
- Etudier la mortinatalité et la mortalité infantile dans la descendance des personnes atteintes de DM au SLSJ.

Tableau I.3

Principaux signes cliniques de la forme congénitale de la dystrophie myotonique.

Hydramnios
Diminution des mouvements foetaux
Faiblesse faciale bilatérale
Hypotonie
Retard mental
Retard du développement moteur
Détresse respiratoire néonatale
Difficultés d'alimentation

CHAPITRE II

FECONDITE DANS LA DYSTROPHIE MYOTONIQUE: UNE ETUDE CAS-TEMOINS AU SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA).

[Fertility in myotonic dystrophy: A case-control study in Saguenay-Lac-St-Jean (Québec, Canada)]

Submitted for publication in "Clinical Genetics".

II.1. RÉSUMÉ

La dystrophie myotonique (DM) est une maladie autosomale dominante qui a une prévalence élevée au Saguenay-Lac-St-Jean. Une étude cas-témoins de 373 personnes atteintes de DM mariées dans cette région entre 1855 et 1971 a été réalisée pour déterminer si leur fécondité était influencée par la maladie. Six paramètres démographiques, à savoir le nombre d'enfants, l'âge au mariage, l'âge à la naissance du premier et du dernier enfant, l'intervalle entre le mariage et la naissance du premier enfant et l'intervalle entre les naissances successives, ont été étudiés. Le nombre moyen d'enfants nés des personnes atteintes n'est pas significativement différent de celui des témoins ($p>0,05$). Cependant, les hommes atteints de DM ont eu plus d'enfants que les femmes atteintes bien qu'ils aient commencé à retarder leur mariage dès 1921. La fécondité a décliné substantiellement dans le groupe DM et le groupe contrôle durant la période d'observation Ce changement reflète le déclin de la fécondité des Canadiens français en général durant cette période, surtout après 1940.

II.2. ABSTRACT

Myotonic dystrophy (MD) is an autosomal dominant disorder that has a high prevalence in Saguenay-Lac-St-Jean. A case-control study of 373 MD patients married in this region between 1855 and 1971 was conducted to determine whether their fertility was affected by the disorder. Six demographic parameters, that is the number of children, the age at marriage, the ages at the time of birth of the first and the last child, the interval between the marriage and the birth of the first child, and the interval between consecutive births, were analyzed. The mean number of children born to MD and control individuals was not different ($p>0.05$). However, MD males had more children than MD females although they have started delaying their marriage since 1921. Fertility fell significantly in both the MD and control groups during the period of observation. This change reflects the decline in fertility of French Canadians in general during this period, but mainly after 1940.

II.3. INTRODUCTION

Myotonic dystrophy (MD), an autosomal dominant disorder, is the most frequent form of muscular dystrophy in adulthood [1]. Its prevalence in Saguenay-Lac-St-Jean (SLSJ) is estimated at 1 in 529 inhabitants [2]; this is the highest prevalence reported thus far.

The SLSJ region is a geographically isolated area located in the northeastern part of Quebec opened to the white settlement in 1838. Its historical, demographic, and genetic characteristics have been described in full detail elsewhere [3,4].

The genealogical reconstruction of 746 MD patients from SLSJ has already shown a common ancestor couple; an homogeneous mutation is presumed among this affected population [2]. Recent data on linkage disequilibrium between the MD locus and RFLPs on chromosome 19 are also compatible with a unique mutation segregating in this population [5,6].

Two studies on fertility in the MD affected population of SLSJ have already been conducted, one on 218 living patients without comparison with control groups [7], the other on 85 ancestors presumably carriers of the MD gene [8-10].

The present report, based on a case-control study, analyzes the fertility of 373 MD individuals living or having lived in Saguenay-Lac-St-Jean since 1838.

II.4. MATERIAL AND METHODS

Population

The families affected with MD were identified through the medical charts kept at the "Clinique des maladies neuro-musculaires" (CMNM) at the "Hôpital de Chicoutimi". The pedigree of each proband was drawn by the staff working at the clinic from a family history questionnaire filled out with the help of the family members [2]. This step allowed the recognition of affected, screened, and suspected individuals over 3 to 4 generations in most of the pedigrees.

An individual was classified as affected if he displayed the caracteristic features of MD at the neuromuscular examination, electromyography and lens examination [2,11]. An individual was classified as screened when he had a family history of MD and showed the typical manifestations of the disorder which were observed by a medical student [2]. If an individual was not seen by a health professional but said to display the typical signs of the disorder by other family members, he was then classified as suspected.

Methodology

The date and place of marriage of each affected, screened or suspected individual identified in these MD pedigrees were searched in the computerized register of the SLSJ population developed and maintained at SOREP. This registry contains all the birth, marriage, and

death records of the Catholic French speaking population of the region from 1838 till 1986. Other informations such as date and place of the events, and occupation of the men are also recorded [12].

A total of 373 affected, screened and suspected MD individuals were found to be married in SLSJ between 1855 and 1971 and to have a complete reproductive history. Subsequently, the whole period (1855-1971) was divided in 11 periods, that is 1855-1870, 9 periods of 10 years each up to 1960, and 1961-1971, to study the evolution of fertility. The reproductive history was considered to be complete if the period of observation following the marriage was at least 25 years long or if it was ended by the death of the MD spouse. However, although the period of observation was shorter than 25 years, the marriages celebrated between 1961 and 1971 were also included in this study (minimum period of observation : 16 years). No marriage after 1971 was kept.

A total of 155 individuals from these MD pedigrees who were considered at risk during their investigation at the CMNM and for whom a complete reproductive history was available were also included in the study (so-called normal group).

Three other control groups matched to the marriages of the 373 affected, screened or suspected MD individuals were created using the computerized SLSJ population register. The matching criteria were: to be French Canadians of Catholic faith, to be married within the same year and parish as the MD individuals, and to have the same

socioeconomic status (as defined by the husband's occupation). Three groups rather than one were created to minimize a possible sporadic high variation in the data. These control groups were chosen at random in the register.

However, the patients identified at the CMNM were only those in which families the MD gene has been transmitted over the generations for the last centuries [2]. Therefore, in each generation, but the most recent, of every MD pedigree, at least one affected, screened or suspected MD individual had a child with MD. Moreover, depending upon the generation considered, the latter got married and had an affected child. Therefore, for each generation by pedigree, one or both conditions needed to be met by at least one individual in every control group. This procedure helped decrease the bias of overestimation of fertility in the target group usually associated with this type of case-control study [13]. The criteria regarding the length of observation of the control couples were the same as those used for the MD couples.

Several demographic parameters were studied; these are the number of children, the age at marriage, the ages at the time of birth of the first and the last child, the interval between the marriage and the birth of the first child, and the interval between consecutive births.

Data relating to the MD, normal and control groups were recorded in a VAX785 computer at the University of Quebec at Chicoutimi using Datatrieve, a database software. The statistical analyses were performed using the Student's t test and the analysis of variance.

II.5. RESULTS

The population under study included 155 normal individuals (84 males and 71 females) married between 1921 and 1971, 373 MD individuals (172 males and 201 females) married between 1855 and 1971 and three control groups of 373 individuals each. Of the 373 MD individuals, 152 (53 males and 99 females) who got married between 1911 and 1971 were classified as affected, 78 (42 males and 36 females) married between 1881 and 1971 as screened and 143 (77 males and 66 females) married between 1855 and 1971 as suspected.

In a first step, no statistically significant differences were found between the affected, screened, and suspected MD individuals in any of the 11 time periods for any of the 6 parameters studied (ANOVA, $p>0.05$). Therefore, these three categories were merged into a unique MD group. Furthermore, no statistically significant differences were found between the three control groups for any of the 6 demographic parameters considered (ANOVA, $p>0.05$); these three groups were then pooled into only one control group.

Table 1 shows the mean values of 6 demographic parameters by groups of individuals married between 1855 and 1971. The analysis of variance done on all individuals, males, and females failed to reveal significant differences between the three groups in the age at marriage, the age at the time of birth of the first child, the interval between the marriage and the birth of the first child, and the interval between consecutive births ($p>0.05$). However, significant differences between

the normal, MD, and control groups were found in the number of children and the age at the time of birth of the last child ($p<0.001$); the Scheffe method showed that the normal group significantly differed from the other two groups ($p<0.05$).

Figure 1 shows the evolution of the six demographic parameters by groups and by periods of marriage. A similar pattern for all six parameters was observed for the three groups (normal, MD, control). The analysis of variance showed significant differences in each group considered when comparing the 11 periods for all 6 parameters ($p<0.05$) except for the mean age at marriage. No significant differences were found in the age at marriage between the 11 periods in the normal group (ANOVA, $F=1.06$, $p=0.38$), nor in the control group (ANOVA, $F=2.0$, $p=0.31$) whereas there was a significant difference in the MD group (ANOVA, $F=3.53$, $p=0.0002$). Figure 1.B shows that the increase in the mean age at marriage is more important in the MD group than in the normal and control groups; this increase is mainly due to an increase in the mean age at marriage of the males (ranging from 20.8 to 29.1 years) rather than of the females (ranging from 17.7 to 23.3 years)

Comparisons between males and females were also performed in every group for each of the six demographic parameters (Table 1). A significant difference was found in the mean number of children between males and females in the MD group ($p<0.001$) and in the control group ($p<0.01$), males having had a higher mean number of children than females in both groups. No difference was found between sexes in the normal group ($p=0.39$). Significant differences were found in the mean

age at marriage and the mean ages at the time of birth of the first and the last child between sexes in all groups considered ($p<0.001$). No significant differences were found between males and females in the mean interval between marriage and the birth of the first child, neither in the mean interval between births ($p>0.05$). In particular, the mean interval separating the successive births and the mean interval between the marriage and the first birth were respectively 26 and 4 days shorter in MD females than in MD males.

II.6. DISCUSSION

A reduced fertility in myotonic dystrophy has been found by most workers; they reported the relative fertility of affected over unaffected or controls to be close to 0.75 of the normal fertility [1, 14-16]. However, it is likely that these studies tended to preferentially recognize the more severely affected and, therefore, the less fertile [1]. Moreover, since these studies were performed in different populations, it is also possible that these MD individuals carried different mutations, which may have different effects on their fertility. In this regard, the SLSJ region offers a unique opportunity as it is believed that only one mutation segregates in this population [2,5,6].

Veillette et al. [7,17] were the first to conduct a study on fertility in myotonic dystrophy in SLSJ based on 218 affected individuals followed at the "Clinique des Maladies neuro-musculaires". They found that married MD males were more fertile than MD females (4.18 and 2.0 children/couple respectively) [7]. However, there was a

considerable decline in marriage eligibility for men, which did not exist for women [7]. If one considered the overall fertility of MD males (married and non married), then their fertility was lower than in females (1.43 and 1.76 children/couple respectively) [7].

Bouchard et al. [8,9] and Roy et al. [10] conducted an other study based on the parents of the oldest affected, screened or suspected individual in each pedigree (N=85). Two control groups were matched on the MD group. The mean number of children in the MD group was not significantly different from that in both control groups.

The study of fertility in hereditary diseases is usually very difficult because of the pitfalls involved in the design of the control groups [13]. We tried to minimize the bias by carefully matching the controls, notably on the socio-economic status of the couple, which is an important factor in the decision-making of having a small or large family. Also, since in each MD pedigree, at least one affected, screened, or suspected MD individual in every generation had an MD child, the same situation was duplicated with control groups which were created by pedigree and by generation.

Studying fertility in myotonic dystrophy is even more difficult because of the extreme variability in the severity and the age at onset of the disorder [11]. Those who married are presumably those who are less affected and/or have an older age at onset. Therefore, such study would tend to estimate the fertility of the less affected MD group. Indeed, based on a muscular disability rating scale developed at the

CMNM [11], it was shown that more severely affected individuals had fewer children than those with minor signs. The mean number of children born to individuals with grade 4 (patients with mild or moderate proximal weakness) was lower than that of individuals with grade 2 (patients with minimal signs showing no distal weakness) and grade 1 (asymptomatic patients in whom the diagnosis was confirmed by EMG, slit-lamp examination or DNA analysis). The mean number of children born to patients with grade 4 was 2.2 (SD: 2.0) compared to 3.5 (SD: 3.1) in grade 2 and 4.4 (SD: 3.2) in grade 1 (ANOVA, $F=3.81$, $p=0.028$). Therefore, although the number of patients included in this study who were graded is small, it is most likely that the MD gene is transmitted over successive generations through less affected individuals. The results reported by Veillette et al. [7, 17] and those found in this study are difficult to be compared because the populations studied by both groups were quite different. Indeed, in the latter study, only 32% of the 373 MD individuals married after 1961 whereas, in the study by Veillette et al., this proportion was close to 70%. Therefore, the present study gives a better estimate of several demographic parameters in a historical perspective. This is also why the present study included screened and suspected MD individuals, in addition of increasing the size of the population considered, although their diagnosis was not confirmed by a neurologist.

This study is based on MD individuals who married. Therefore, it does not take into consideration those MD individuals who died in infancy or childhood (notably the congenital forms) as well as those who did not find a spouse. Indeed, the individuals in whom the first

symptoms appeared in infancy or childhood were less likely to marry, if not at all. It is impossible to estimate from the SLSJ population register which proportion of MD individuals was not eligible for marriage. In these computerized reconstructed families, not finding the marriage of an individual means either that he did not marry, or that his marriage record was lost, or that he emigrated from the SLSJ region. The marriage rate was studied by Veillette et al. [7, 17]. They found that MD males were less likely to marry than MD females ($p<0.05$). However, this difference appeared to be a recent phenomenon. Indeed, no difference was found between MD males and females aged 55 years and older (which corrresponds more or less to marriages celebrated in the 1950s) whereas a significant difference was found between males and females aged 45 and younger (corresponding to marriages in the 1960s and 1970s) [7, 17]. If we assume that there is no sex distortion in the segregation of myotonic dystrophy in SLSJ, an equal number of males and females should have married for each period considered. In this study, the proportion of marriages involving a MD male over the total number of marriages of MD individuals ranges from 35 to 61.1% (mean value: 50.5%) from 1855 to 1960; however, for the period 1961-1971, its value was 23.3% (14/46). We know from interviews with elderly people that, until recently, there has been a very strong social pressure to get married and to have children.

Veillette et al. [7,17] reported that the age at marriage of the MD males was higher than that of the MD females, the gap between both mean ages increasing over the generations. Our results confirm this trend but also show that this is a recent phenomenon. Indeed, the mean

ages at marriage for MD males and control males during the period 1855-1871 were 20.8 and 22.2 years, during the period 1911-1920, 22.1 and 24.1 years, and during the period 1961-1971, 29.1 and 24.0 years respectively. For the same periods, the mean ages at marriage for MD females compared to control females were 17.7 and 20.0 years, 21.5 and 20.2 years, and 23.6 and 22.3 years. However, the mean number of children fathered by MD males married during the period 1961-1971 was not statistically different from that of their controls (2.07 and 1.95 children respectively, $p>0.05$). In fact, although the mean age at marriage of the MD males was significantly higher than of the control males in the last five periods (starting in 1921) ($p<0.001$), the mean number of children fathered by these MD males was not significantly lower than those fathered by the control males during the same periods ($p>0.05$). Furthermore, our results show that the mean age at marriage is higher in males than in females in all three groups (normal, MD, and control) ($p<0.001$).

Our results also confirm that MD males had more children than MD females, as previously reported by Veillette et al. [7,17], but so did the control males. Such a result might be quite surprising. A high frequency of testicular tubular changes has been reported in myotonic dystrophy, even in mildly affected individuals [1]. Therefore, one might expect a high degree of male infertility in MD. Indeed, most series have found a higher number of unmarried males than females as well as a reduction in fertility of males compared to females [1,14-16]. In fact, our results do not confirm those previous studies. Since we do not know if the MD males in SLSJ have testicular tubular changes, and, if so, if these

changes happen early in the course of the disease, it is difficult to explain these differences.

Because of an older age at marriage and a greater number of children, it is obvious that the mean ages at the time of birth of the first and the last child should be higher in males than in females in the MD and control groups. The number of children and the age at the time of birth of the last child were significantly lower in the normal group than in the MD and control groups (table 1). Such a result is due to the fact that no individual in the MD pedigrees married before 1921 were said to be normal following a complete neurological examination at the CMNM. It is during the period 1921-1930, but more obviously during the following period (1931-1940) that changes in the reproductive behaviour can be observed in the MD and control populations (figure 1). The most dramatic changes occurred in the mean number of children, the mean age at the time of birth of the last child, and the mean interval between consecutive births (figure 1). The fertility fell significantly in all three groups during the period of observation, and more particularly after 1940. Such decline in the fertility was already noted in a previous case-control study performed on couples heterozygotes for the tyrosinemia gene in SLSJ [13]; these changes reflect the decline in fertility of French Canadians in general during this period [18].

Three reports on reproductive loss in women with myotonic dystrophy have appeared in the literature [1,19,20]. They showed an abortion rate ranging from 17 to 32.5 per 100 livebirths, which is 2 to 3 times above that in the general population rate of around 10%. Although

such a difference should be statistically significant, the increase in the abortion rate might not be enough to influence the mean interval between the time of marriage and the time of birth of the first child, neither the mean interval between consecutive births. This presumably explains why no significant differences in these two parameters were obtained between the MD and control groups, neither between males and females.

In conclusion, this study finds no differences in the reproductive behaviour of the myotonic dystrophy population during the period 1855-1971. Although MD males recently started delaying their marriage, such a decision does not appear to have influenced the number of children they fathered.

II.7. REFERENCES

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II.8. TABLE

Table 1. Comparison of six demographic parameters by groups of individuals married between 1855 and 1971 in Saguenay-Lac-St-Jean

	NORMAL			MD			CONTROL		
	M + F	M	F	M + F	M	F	M + F	M	F
Nr of children (SD)	3.8 (3.4)	4.0 (3.4)	3.5 (3.3)	6.2 (4.5)	7.3 (4.3)	5.3 (4.4)	6.3 (4.5)	7.2 (4.5)	5.6 (4.4)
Age at marriage years (SD)	23.6 (3.8)	24.9 (3.3)	22.0 (3.7)	23.6 (4.7)	25.1 (5.0)	22.3 (4.0)	23.1 (4.5)	24.6 (4.1)	21.7 (4.3)
Age at time of birth of first child-years (SD)	24.8 (4.0)	26.4 (3.7)	22.9 (3.5)	24.5 (4.4)	26.2 (4.5)	23.0 (3.7)	24.3 (4.3)	25.9 (4.1)	22.9 (3.9)
Age at time of birth of last child-years (SD)	32.5 (7.0)	34.6 (7.2)	29.9 (6.0)	36.8 (8.0)	40.2 (7.0)	33.6 (7.5)	36.5 (8.0)	39.4 (7.8)	33.9 (7.1)
Interval marriage/first child days (SD)	551 (569)	569 (642)	533 (474)	478 (683)	482 (766)	478 (595)	464 (620)	453 (409)	474 (763)
Interval between children days (SD)	617 (237)	646 (212)	588 (263)	653 (281)	668 (281)	642 (281)	650 (266)	664 (248)	639 (281)

M = males F = females
SD = standard deviation

II.9. FIGURE

Figure II.1: Evolution of six demographic parameters by groups and by periods of marriage. The full period 1855-1971 was divided in 11 periods as described in the methodology.

A Number of children

B Age at marriage

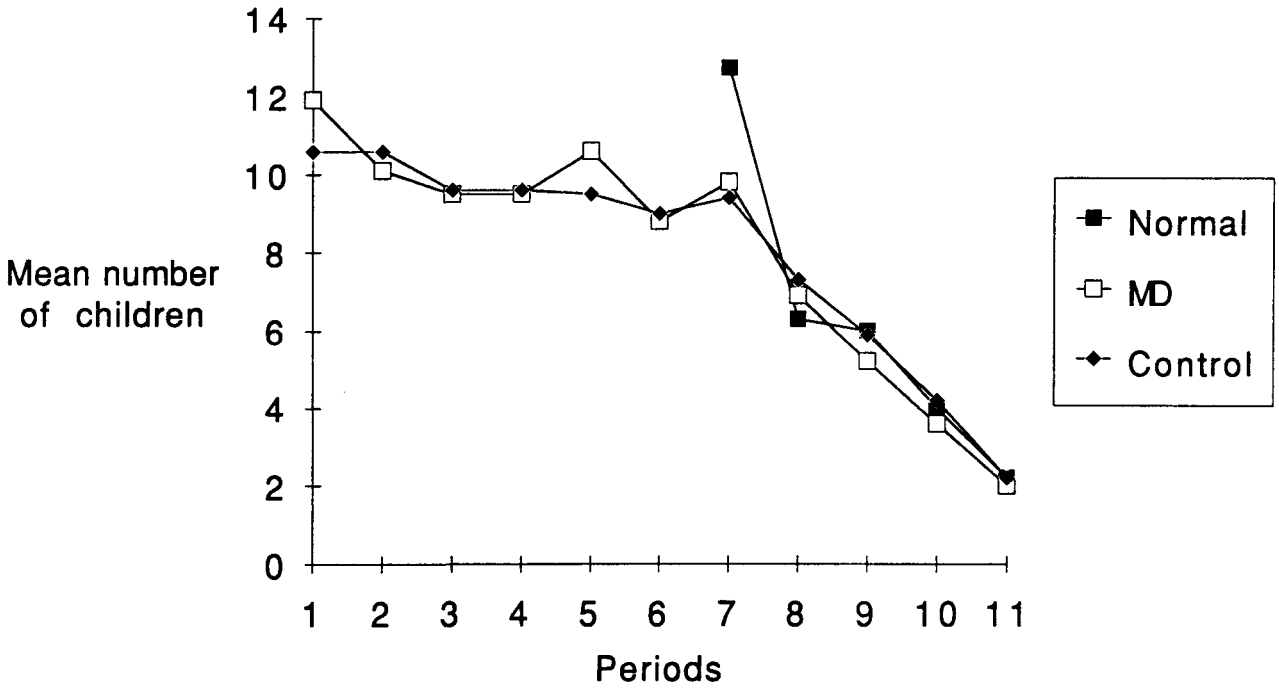
C Age at the time of birth of the first child

D Age at the time of birth of the last child

E Interval between the marriage and the birth of the first child

F Interval between consecutive births

Period	1	1855-1870	7	1921-1930
	2	1871-1880	8	1931-1940
	3	1881-1890	9	1941-1950
	4	1891-1900	10	1951-1960
	5	1901-1910	11	1961-1971
	6	1911-1920		


Mean number of children
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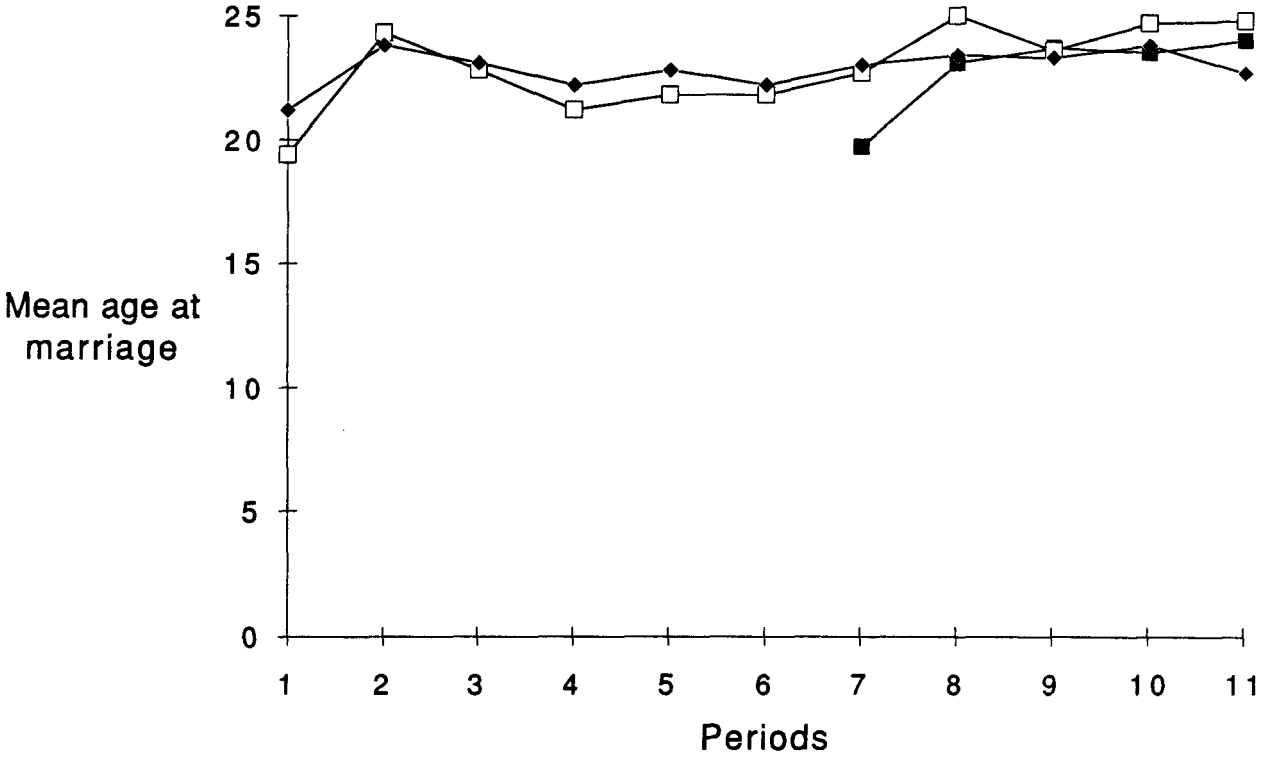
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11
Periods
Normal
MD
Control


Mean age at marriage
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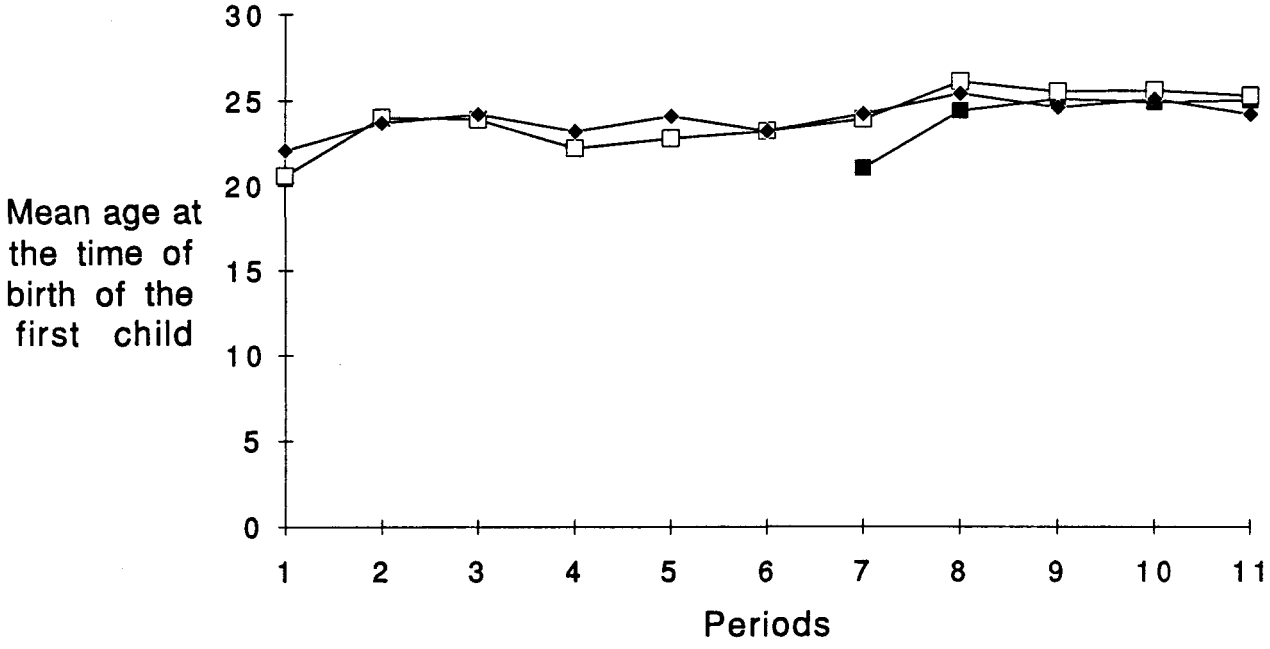
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
Periods


Mean age at the time of birth of the first child
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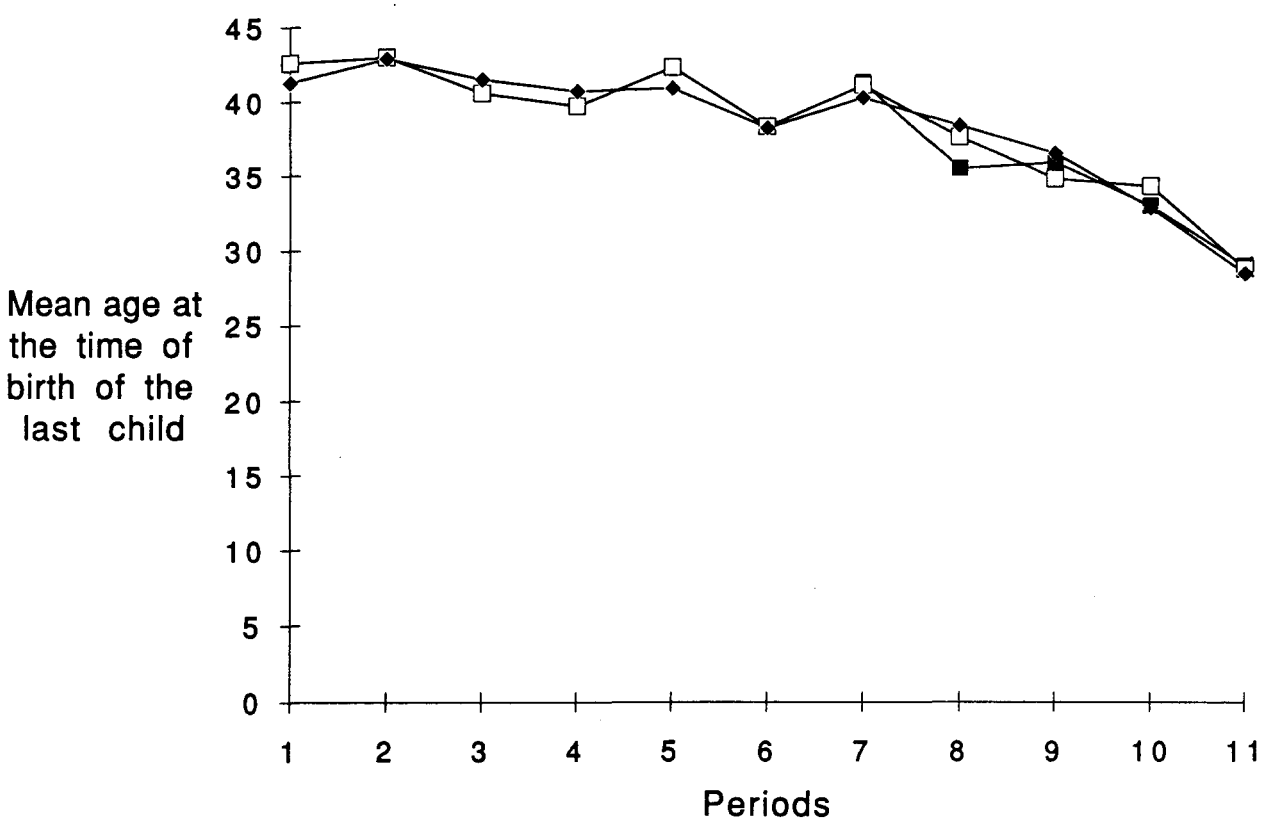
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
Periods


Mean age at the time of birth of the last child
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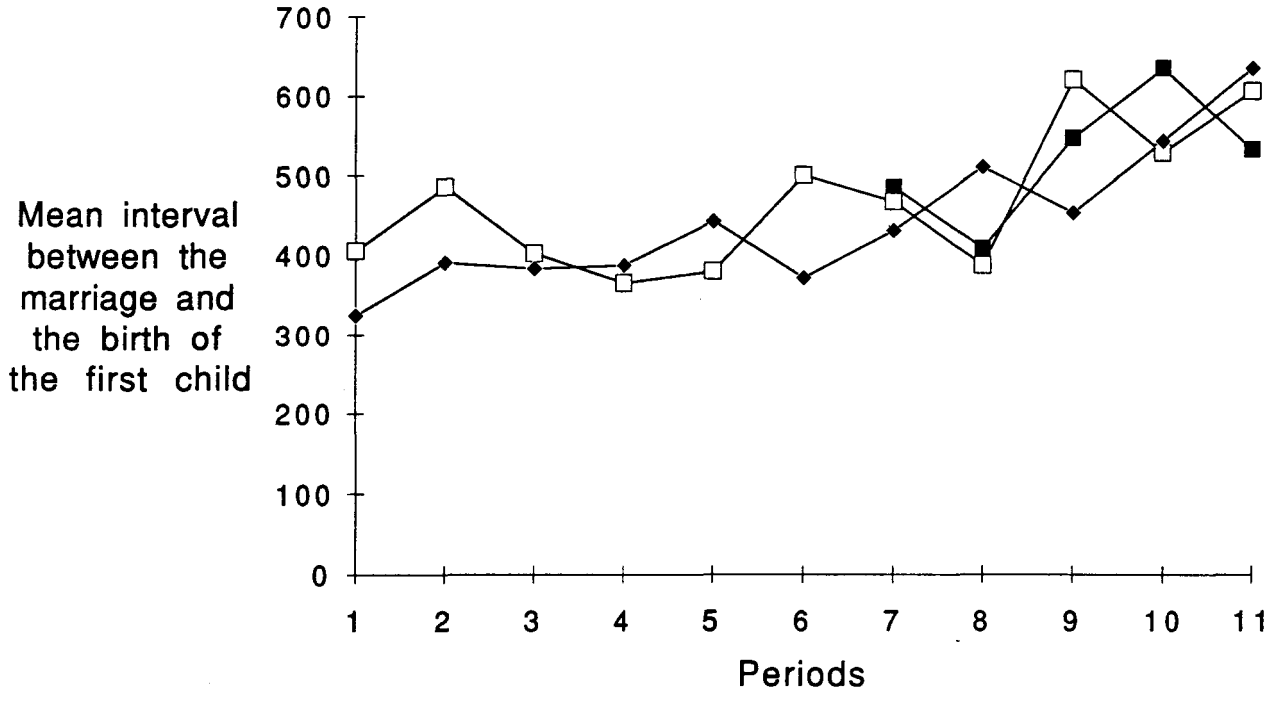
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
Periods


Mean interval between the marriage and the birth of the first child
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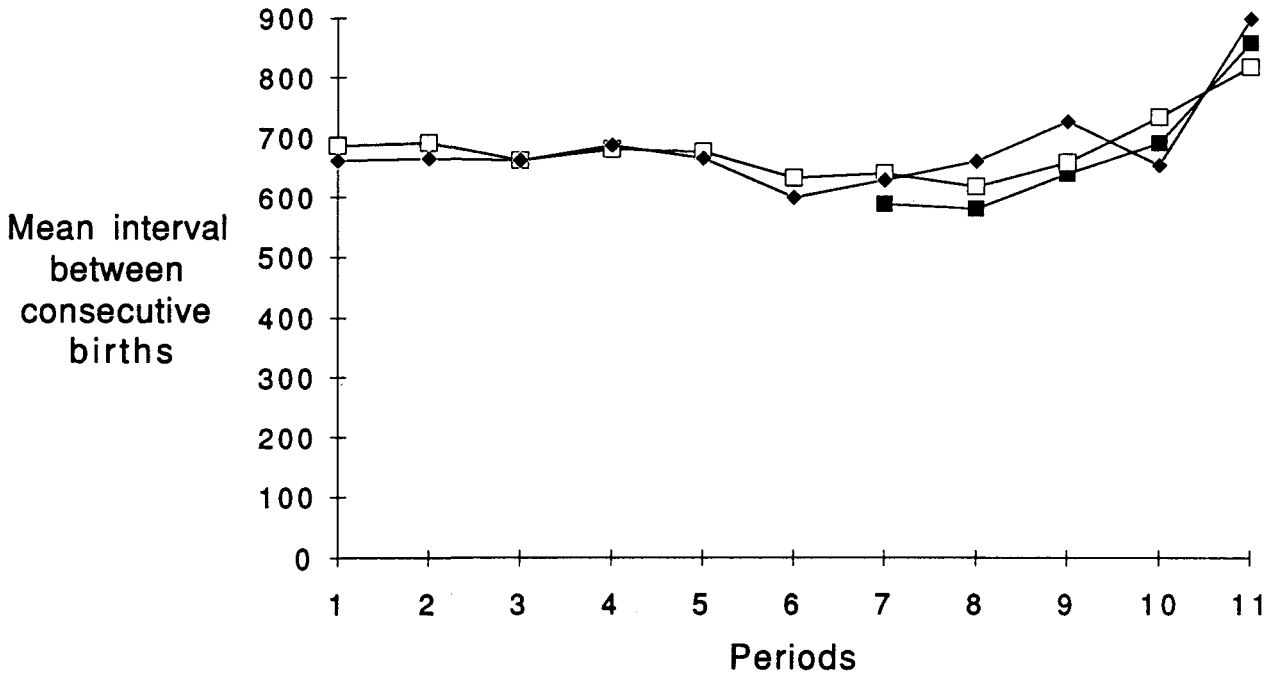
600
500
400
300
200
100
0
1
2
3
4
5
6
7
8
9
10
11
Periods


Mean interval between consecutive births
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800
700
600
500
400
300
200
100
0
1
2
3
4
5
6
7
8
9
10
11
Periods

CHAPITRE III

MORTALITE INFANTILE DANS LA DYSTROPHIE MYOTONIQUE: UNE ETUDE CAS-TEMOIN AU SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA)

[Infant mortality in myotonic dystrophy: A case-control study in Saguenay-Lac-St-Jean (Quebec, Canada)].

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III.1. RÉSUMÉ

Une étude cas-témoins de la mortalité infantile parmi les enfants de 373 personnes atteintes de dystrophie myotonique (DM) vivant ou ayant vécu au Saguenay-Lac-St-Jean depuis 1838 a été réalisée. Une augmentation statistiquement significative a été trouvée dans le taux de mortalité durant la première semaine parmi les enfants des mères atteintes de DM (57,5‰) comparativement aux taux de mortalité des enfants issus de mères témoins (34,8‰) et de pères atteints (39,1‰) ($p<0,01$). Le taux de mortinatalité n'était pas augmenté. Le taux des décès survenant après la première semaine a décliné substantiellement dans les deux groupes durant la période d'observation.

III.2. ABSTRACT

The infant mortality among children born to 373 individuals with myotonic dystrophy (MD) living or having lived in Saguenay-Lac-St-Jean since 1838 was analyzed using a case-control approach. A statistically significant increase was found in the rate of deaths during the first week among children born to MD mothers (57.5‰) compared to control mothers (34.8‰) and MD fathers (39.1‰) ($p<0.01$). The stillbirth rate was not increased. The rate of mortality after the first week fell significantly in both MD and control groups during the period of observation.

III.3. INTRODUCTION

Myotonic dystrophy (MD) is an autosomal disorder that has a high prevalence in Saguenay-Lac-St-Jean (SLSJ), a geographically isolated region of northeastern Quebec opened to the white settlement in 1838 [1]. An homogeneous mutation in the MD gene is presumed among this affected population [1-3].

Few studies on infant mortality in MD have been reported. Only four reports, including one from SLSJ, have appeared in the literature [4-7]. This prompted us to analyze the infant mortality among the children of 373 MD individuals living or having lived in SLSJ since 1838.

III.4. MATERIAL AND METHODS

The population under study and the methodology have been described in full details in a previous publication [8]. Briefly, the 373 MD individuals who were the basis of this study were divided in 152 affected, 78 screened, and 143 suspected individuals. All of them married in SLSJ between 1855 and 1971; this period of observation was divided in 11 periods to allow a study on the evolution of infant mortality. The MD individuals needed to have a complete reproductive history to be included in the study.

Three control groups matched to the marriages of the 373 MD individuals were created using the computerized SLSJ population register. A total of 155 non affected (so-called normal) individuals from

the MD pedigrees were also included in the study.

Data on mortality were extracted from the SLSJ population register and computerized in a dataset. All the deaths up to age 15, including the stillbirths, were recorded. For analysis purposes, they were divided in 7 categories: stillbirths, livebirths deceased during the first week, deaths between 8 and 28 days, deaths between 29 and 365 days, deaths between 1year 1day and 5 years, deaths between 5years 1day and 10 years, and deaths between 10years 1day and 15 years.

The statistical analyses were performed using the chi-square test.

III.5. RESULTS

In a first step, no statistically significant differences were found between the affected, screened, and suspected MD individuals for any of the 7 categories of mortality considered ($p>0.05$). Therefore, these three MD categories were merged into one MD group. Furthermore, no statistically significant differences were found between the three control groups for any of the 7 categories of mortality analyzed ($p>0.05$); they were pooled into one control group.

Table 1 shows the rate of mortality expressed in per thousand births by groups of individuals married between 1855 and 1971 and by categories of mortality. The statistical analyses done on all the individuals, males, and females failed to reveal significant differences between the three groups (normal, MD, and control) in the rate of

stillbirths, and the rates of mortality between 8 and 28 days and after 5 years (from 5years 1day to 10 years and from 10years 1day to 15 years) ($p>0.05$). However, significant differences between the normal, MD, and control groups were found in the rate of mortality between 29 and 365 days as well as between 1year 1day and 5 years ($p<0.05$); in both categories of mortality, the rate was lower in the normal group while it was similar in the other two groups (MD and control).

A highly significant difference was found in the rate of mortality of children born to females during the first week (chi-square=10.78, 2df, p=0.005). The rates of mortality during the first week were respectively 39.7‰ and 34.8‰ in the female normal and control groups but 57.5‰ in the MD female group. No significant difference was found in the rate of mortality of children born to males during the first week (chi-square=0.51, 2df, p=0.77).

Table 1 also shows that the rate of mortality in each group and sex was higher between 29 and 365 days than before (8 to 28 days) and after (1year 1day to 15years); in fact, a steady decline in the mortality rate was observed after the first month of life.

Comparisons between males and females were also performed in every group for each of the 7 categories of mortality (table 1). No significant differences in the mortality rate were found in the categories of mortality and the groups considered ($p>0.05$), except in the MD group for livebirths deceased during the first week. Indeed, the rates for males and females were 39.1‰ and 57.5‰ respectively (chi-square=

4.29, 1df, p=0.038).

The evolution of the mortality rate was also studied for each group and mortality category during the whole period of observation (1855-1971). A decline in the mortality rate was found for deaths occurring after 8 days of life ($p<0.05$). This decline was particularly evident among the children of individuals married after 1921. No decline in the rate of stillbirths was observed in the normal group ($p>0.05$), the MD group ($p>0.05$), nor the control group ($p>0.05$) as well as in the mortality rate of liveborns during the first week ($p>0.05$).

III.6. DISCUSSION

To the best of our knowledge, this is the first extensive study on infant mortality in a large population of MD patients presumed to carry a unique mutation using a case-control approach. A study conducted by Bouchard et al. [4] in SLSJ on 85 individuals presumably affected with myotonic dystrophy showed a neonatal mortality rate of 69.6‰ compared to 42.4‰ in controls. The infant mortality rates were respectively 131.4‰ and 103.2‰. Unfortunately, the analysis was not performed according to the sex of the MD individuals. Furthermore, the infant mortality was not divided into categories but it appears that the higher infant mortality observed in the MD group compared to the control group is the result of the higher neonatal mortality rate in the MD group.

An increased mortality among offspring of mothers with

myotonic dystrophy was noted by several workers [9-12]. This increased mortality was attributed, at least in part, to the congenital form of the disease [7]. In fact, Harper [5] showed that, in 24 neonatal deaths among sibs of patients with congenital MD, 23 occurred during the first week of life. This observation is corroborated by our results which showed a significant increase in the mortality rate of liveborns in the first week from MD mothers, but not from MD fathers. Using the neuromuscular disability scale developed at the "Clinique des Maladies neuro-musculaires" of the "Hôpital de Chicoutimi" [13], we tried to see whether there was a relation between the risk of early infant death and the severity of the disease in the mother. No significant difference in the mortality rate during the first week of life was found between asymptomatic mothers with no muscle weakness (grade 1) or with a slight distal muscle involvement (grade 2) or with a mild or moderate proximal muscle involvement (grade 4) ($p>0.05$). However, it should be noted that this series was very small (28 MD females) and that the age at onset was not taken into account.

The rate of stillbirths was not found to be increased in MD women compared to MD men and control females; this result confirms earlier observations by Harper [5] and O'Brien and Harper [6].

A peak in the mortality rate was noted for those deaths occurring between 29 and 365 days after birth; since it was observed in all the groups, it is not related to the presence of the MD gene but is presumably the consequence of gastro-enteritis and other infections following the ablactation. No decline in the rate of stillbirths and the

mortality rate of liveborns during the first week was observed during the period 1855-1971; indeed, mortinatality and mortality during the first week are believed to be mainly due to genetic (endogenous) causes. Therefore, an improvement in child care during the period of observation would result in a decrease of the mortality related mainly to exogenous causes, that is mainly after 7 days, but not before.

The rate of spontaneous abortion was found to be 2 to 3 times higher in women with myotonic dystrophy than in non-affected females or in the general population [5-7]. Unfortunately, this aspect of reproductive loss could not be analyzed in SLSJ because the study was based on data extracted from a population register and not from interviews in the affected families. This is also the reason why we cannot confirm whether the higher rate of mortality during the first week of life was the result of deaths of children with the congenital form of the disease.

In conclusion, this case-control study confirms that there is a significant risk of early death (during the first week) in children born to mothers with myotonic dystrophy. This risk combined to a higher risk of spontaneous abortion should be kept in mind when counselling MD females wanting to embark on a pregnancy. Since it was shown in a previous study that the fertility of this MD population was not decreased compared to the general population of SLSJ [8], compensative reproduction presumably occurred in this population.

III.7. RÉFÉRENCES

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III.8. TABLE

Table 1. Rates of infant mortality in myotonic dystrophy in Saguenay-Lac-St-Jean.

	NORMAL			MD			CONTROL		
	M + F	M	F	M + F	M	F	M + F	M	F
Nr of children	590	338	252	2314	1253	1061	7119	3729	3390
Stillbirths (in ‰)	28.8	38.5	15.9	12.5	9.6	16.0	20.5	24.4	6.2
First week (in ‰)	44.1	47.3	39.7	47.5	39.1	57.5	38.8	42.4	34.8
8 - 28 days (in ‰)	3.4	3.0	4.0	11.2	12.0	10.4	12.6	12.9	12.4
29 - 365 days (in ‰)	22.0	26.6	15.9	52.7	54.3	50.9	62.1	61.4	62.8
1y 1d - 5y (in ‰)	13.6	8.9	9.8	30.3	29.5	31.1	33.2	32.3	33.0
5y 1d - 10y (in ‰)	5.1	5.9	4.0	11.2	11.2	11.3	9.0	9.4	8.6
10y 1d - 15y (in ‰)	1.7	0.0	4.0	6.9	5.8	8.5	6.5	5.9	7.1

M = males
F = females
y = year
d = day

CONCLUSION GÉNÉRALE

Au terme de cette recherche, il est évident que pendant près de 110 ans (1850-1960), les personnes atteintes de dystrophie myotonique ont eu un comportement reproducteur semblable à celui de la population du Saguenay-Lac-St-Jean.

En effet, nos résultats montrent qu'elles ont eu autant d'enfants, qu'elles se sont mariées dans les mêmes proportions et au même âge et que leur période de reproduction a été aussi longue que dans la population générale. De plus, à l'exception des enfants de mères atteintes qui ont un risque nettement accru de décéder pendant la première semaine après la naissance, la mortalité infantile était semblable dans le groupe cible et dans la population générale. Enfin, le taux élevé d'avortements spontanés rapportés par d'autres chercheurs chez les mères atteintes de dystrophie myotonique ne semble pas avoir eu de répercussion sur le nombre d'enfants qu'elles ont eus. Un phénomène de reproduction compensatrice a vraisemblablement existé au Saguenay-Lac-St-Jean.

Il serait évidemment intéressant d'étudier et de quantifier, dans quelques années, l'impact sur les comportements reproducteurs de cette population cible qu'ont l'introduction d'une contraception efficace, le

conseil génétique, le diagnostic prénatal ainsi que la détection des porteurs asymptomatiques.

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